

CLAIMS:

1. A method of reducing proliferation of cells, comprising:
 - 5 a) exposing said cells to a composition comprising a nucleic acid encoding at least one polypeptide comprising an amino acid sequence with the transport function of herpesviral VP22 protein, said polypeptide being coupled to at least one functionally active amino acid sequence, wherein the functionally active amino acid sequence is a protein or peptide which can regulate cell cycle progression, or functional analogue
10 thereof; and
 - b) exposing said cells to at least one agent to further stimulate cell death, said agent being selected from: drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, agents which increase cellular sensitivity to DNA damage, and
15 cytotoxic amounts of radiation.
2. A method according to claim 1, wherein said cells are hyperproliferating cells.
- 20 3. A method according to claim 1, wherein said coupled polypeptide can induce apoptosis, or can arrest cells from the cell cycle.
4. A method according to claim 2, wherein said cells are cancer cells.
- 25 5. A method according to claim 3, wherein said polypeptide is a cyclin-dependent kinase inhibitor.

6. A composition comprising
- (a) a nucleic acid encoding a coupling product between a protein with the transport function of VP22 and a protein which can regulate cell cycle progression; and
- (b) at least one agent to further stimulate cell death, said agent being
- 5 selected from the group consisting of drugs which can induce cell cycle arrest, cytotoxic chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage; in combination with a suitable pharmaceutical excipient.
- 10 7. A method of manufacture of a medicament to reduce cell proliferation comprising formulating a preparation comprising (a) a nucleic acid encoding a coupling product between a protein with the transport function or VP22 and a protein which can regulate cell cycle progression, and (b) at least one agent to further stimulate cell death, said agent being selected from the group consisting of drugs which can induce cell cycle
- 15 arrest, cytotoxic chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage, with a suitable pharmaceutical excipient.
- 20 8. A method of reducing cell proliferation comprising exposing said cells to a preparation comprising:
- (a) a nucleic acid encoding a coupling product between a protein with the transport function or VP22 and a protein which can regulate cell cycle progression; and
- (b) at least one agent to further stimulate cell death, said agent being selected from the group consisting of drugs which can induce cell cycle arrest, cytotoxic
- 25 chemotherapeutic drugs commonly used as part of a treatment of malignant disease, DNA damaging agents, and agents which increase cellular sensitivity to DNA damage, in combination with a suitable pharmaceutical excipient, thereby reducing proliferation of said cells.

9. A method according to claim 1, wherein the polypeptide is coupled to a plurality of functionally active amino acid sequences.

10. A method according to claim 1, comprising further (c) exposing said
5 cells to at least one agent that can prevent export from the cell of any one of the agents administered in a) and/or b), wherein said exposure occurs after step a) and/or step b).

11. A method according to claim 10, wherein said agent that can prevent
10 export from the cell of any one of the agents administered in a) and/or b) is an Acf protein or an inhibitor of the multi-drug resistance protein.

12. A method according to claim 11, wherein said agent is an antisense molecule.

13. The composition of claim 6, further comprising (c) at least one agent that
15 can prevent export from the cell of any one of the agents (a) and/or (b).

14. The method of claim 7, wherein the preparation further comprises (c) at
least one agent that can prevent export from the cell of any one of the agents (a) and/or
20 (b).

15. The method of claim 8, and wherein said preparation further comprises
(c) at least one agent that can prevent export from the cell of any one of the agents (a)
and/or (b).